THE EFFECT OF A SUBCUTANEOUS INJECTION OF CADMIUM SALTS ON THE OVARIES OF ADULT RATS IN PERSISTENT OESTRUS

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The parenteral injection of a small amount of cadmium salts produces massive haemorrhagic necrosis of the gonad in male rats (Pařízek & Žáhoř, 1956; Pařízek, 1960) and an analogous destruction of the foetal part of placentae in pregnant female rats (Pařízek, 1964). However, no changes similar to the complete destruction of these organs were detected in the ovaries of adult female rats injected subcutaneously with the same or even a higher dose of cadmium salts (Pařízek & Žáhoř, 1956; Gunn, Gould & Anderson, 1963; Maekawa, Tsunenari & Yoshitoshi, 1967). In contrast with the sterilizing effect of cadmium in the male, analogous subcutaneous injections of cadmium into female rats (before admission of the male) did not affect fertility (Pařízek, 1957a, 1960).

However, in the prepubertal rats a similar subcutaneous injection of cadmium chloride was reported to induce profound cellular and vascular changes in the ovaries (Kar, Das & Karkun, 1959). Also, as reported briefly elsewhere, extensive haemorrhages and necroses can be produced in the ovaries of adult rats, when cadmium salts are injected subcutaneously into adult non-ovulating rats in persistent oestrus (Pařízek, 1963, 1967) induced by a single injection of androgens or N-anabolic steroids during the first days of post-natal life (Barraclough, 1961; Harris, 1964; Barraclough, 1966). This seems to suggest that ovarian maturation and cyclic ovarian changes connected with ovulation and/or corresponding hormonal regulation could be responsible for the fact that similar ovarian damage was not detected after a subcutaneous injection of cadmium into normal adult rats. A more extensive study of the effect of cadmium on the ovaries of adult rats in persistent oestrus was therefore undertaken.

Adult female rats (Wistar substrain Konárovice), aged 3 to 6 months, were used, in which persistent oestrus had been induced by a single subcutaneous injection of testosterone propionate (Agovirin Spofa) or 19-nortestosterone phenylpropionate (Superanabolon Spofa) given on the 5th day of post-natal life (1-25 mg/rat). Subcutaneous injection of cadmium salts induced quite profound cadmium-specific changes in the ovaries of these rats (Table 1 and Pl. 1, Fig. 1). These very characteristic extensive changes affecting almost the whole organ were not detected after the injection of cadmium salts into normal adult rats or rats which had only been injected with oil (without
hormone) on the 5th day of life (twenty rats). The possibility that parenteral injection of cadmium may produce very much less pronounced changes affecting blood vessels in selected areas of normal adult ovaries, particularly during certain stages of the ovarian oestrous cycle, cannot be excluded, of course, and seems to deserve further attention in the light of the experiments reported here. No qualitative difference was observed between the injection of cadmium chloride or cadmium acetate; a similar injection of mercuric chloride did not produce these changes (Table 1 and Pl. 1, Fig. 2).

In an analogy with the protective effect of zinc (Pařízek, 1957b) or selenium (Kar, Das & Mukerji, 1960; Mason, Young & Brown, 1964) against the toxicity of cadmium in the male gonad, parenteral injection of zinc salts or selenium compounds also protected the ovaries of rats in persistent oestrus from the effect of cadmium (Table 1). It should be mentioned, however, that this protective

<table>
<thead>
<tr>
<th>Group no.</th>
<th>Subcutaneous inj. (m-mole/kg b.w.)</th>
<th>No. of rats</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cadmium chloride (a) 0.02 m-mole</td>
<td>14</td>
<td>Dark purple ovaries 24 hr after cadmium injection: in all ovaries vascular engorgement and extensive haemorrhages localized in the theca folliculi (encircling the follicles) there completely and in the interstitial tissue (Pl. 1, Fig. 1). Massive haemorrhages accompanied by necrosis affecting large areas of ovaries 48 hr after injection. No qualitative difference between the Groups 1a, b and 2a, b.</td>
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<tr>
<td>2</td>
<td>Cadmium acetate (a) 0.02 m-mole</td>
<td>6</td>
<td>Pale ovaries in all rats 24 hr after injection of sublimate. Haemorrhages in ovaries not detected (Pl. 1, Fig. 2)</td>
</tr>
<tr>
<td>3</td>
<td>Mercuric chloride (a) 0.02 m-mole</td>
<td>4</td>
<td>Pale ovaries in all rats, haemorrhages in ovaries not detected.</td>
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<tr>
<td>4</td>
<td>Without injection of cadmium or mercury salts</td>
<td>12</td>
<td>Pale ovaries in all rats, haemorrhages in ovaries not detected.</td>
</tr>
<tr>
<td>5</td>
<td>Cadmium chloride (0.02 m-mole) with zinc chloride (2 m-mole, divided in two equal doses 4 hr before and simultaneously with cadmium)</td>
<td>8</td>
<td>Pale ovaries in all rats 24 hr after cadmium injection: haemorrhages in ovaries not detected. The effect of cadmium not observed.</td>
</tr>
<tr>
<td>6</td>
<td>Cadmium chloride (0.02 m-mole) simultaneously with sodium selenite (0.02 m-mole)</td>
<td>8</td>
<td>Pale ovaries in all rats 24 hr after cadmium injection: haemorrhages in ovaries not detected. The effect of cadmium not observed.</td>
</tr>
<tr>
<td>7</td>
<td>Cadmium chloride (0.02 m-mole); 0.4 ml of saline s.c. 48 hr before cadmium</td>
<td>12</td>
<td>Dark purple ovaries in all rats with typical massive haemorrhages 24 hr after cadmium injection. (Results similar as in Groups 1 and 2). Pl. 1, Fig. 3.</td>
</tr>
<tr>
<td>8</td>
<td>Cadmium chloride (0.02 m-mole) 120 i.u. PMSG in 0.4 ml of saline s.c. 48 hr before cadmium</td>
<td>12</td>
<td>Pale ovaries in all rats 24 hr after cadmium injection; vascular changes detected only highly exceptionally in a very few follicles. Pl. 1, Fig. 4.</td>
</tr>
</tbody>
</table>

Cadmium chloride, cadmium acetate and sodium selenite injected subcutaneously as 0.02 m solutions; zinc chloride as 0.2 m solution. Rats killed by decapitation 24–48 hr after cadmium treatment.
effect of zinc or selenium is not confined to the effect of cadmium on reproductive organs only: both selenium compounds (Pařízek, Šťádalová, Beneš & Babicky, 1968) or zinc salts (Pařízek, Beneš, Kalousková, Šťádalová, Lener, Babicky & Beneš, 1968) affect the survival of rats injected with a large dose (lethal in controls) of cadmium.

Pre-treatment with pregnant mare serum gonadotrophin (pMSG; Equinex Ayerst) proved to be highly effective in preventing the effect of cadmium on the ovaries of rats in persistent oestrus (Table 1 and Pl. 1, Figs. 3 and 4). A similar protective effect of pre-treatment with pMSG (30 i.u.) was observed in another group of eight prepubertal 32-day-old rats. Further experiments in progress are necessary to compare this protective effect of pMSG with other gonadotrophins as well as to show whether gonadotrophins have a similar protective effect in the other reproductive organs known to be sensitive to cadmium. This possibility might be of interest in the light of the fact that cadmium seems to induce peculiar vascular damage in the organs representing target tissue for gonadotrophins.

We should like to express our thanks to Dr J. B. Jewell for the provision of pMSG, Equinex, from Ayerst Laboratories, Mr J. Fiala for the preparation of photomicrographs and to Mr K. Krejčí for technical assistance.

REFERENCES


EXPLANATION OF PLATE 1

Fig. 1. The effect of a subcutaneous injection of cadmium chloride (0·02 m-mole/kg b.w.) in the ovaries of an adult 3-month-old rat in persistent oestrus (induced by an injection of testosterone propionate on the 5th postnatal day): massive haemorrhages in the theca folliculi and in the interstitial tissue 24 hr after cadmium injection. (Formol, Lepehne, haemoglobin stain, haematoxylin, ×50.)

Fig. 2. The ovary of a similar rat in persistent oestrus, at the same age, 24 hr after the subcutaneous injection of mercuric chloride (0·04 m-mole/kg b.w.): haemorrhages in the ovaries not detected. (Formol, Lepehne, haemoglobin stain, haematoxylin, ×50.)

Fig. 3. Massive haemorrhages in the theca folliculi and in the interstitial tissue in a 5-month-old rat in persistent oestrus 24 hr after subcutaneous injection of cadmium chloride (0·02 m-mole/kg b.w.); 48 hr before cadmium, instead of PMSG, solvent (saline) injected only. (Formol, Lepehne, haemoglobin stain, haematoxylin, ×100.)

Fig. 4. The protective effect of pretreatment with PMSG: cadmium chloride (0·02 m-mole/kg b.w.) injected into a 5-month-old rat in persistent oestrus subcutaneously 48 hr after the injection of 120 i.u. PMSG: ovary without haemorrhages 24 hr after cadmium injection. (Formol, Lepehne, haemoglobin stain, haematoxylin, ×100.)